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Review Article

The multiple roles of deubiquitinases in liver cancer

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Abstract: Primary liver cancer ranks the second leading cause of death associated with cancer in the world and therefore a major public health challenge. The mortality rates of liver cancer has been increasing during the past decades with the reality that the alternative therapeutic drugs are not available. Although growing numbers of proteins involved in liver cancer progression have been identified, many of these are not suitable drug targets, which hinders the development of new drugs to cure liver cancer. It is in urgent demand that novel therapeutic approaches should be explored. Deubiquitinases (DUBs), specifically removing ubiquitin chains from the target protein, have showed vital roles for protein homeostasis and quality control by rigidly regulating the balance between ubiquitination and deubiquitination in normal physiology. Recent studies have revealed deregulation or dysfunction of DUBs always associates with cancer and other diseases. Targeting certain DUBs, leading to degradation or loss function of the key oncoproteins, including undruggable ones, seems to provide a potential therapy for cancer patients. In liver cancer, numberous of DUBs are demonstrated to participate in hepatocarcinogenesis, metastasis and so on. Depending on the substrates, some DUBs may suppress liver cancers while others promote. In this review, we primarily summarize the roles of DUBs in liver tumors, and illustrate opportunities for the application of targeting DUBs for cancer therapy.

Keywords: Primary liver cancer, deubiquitinases, cancer therapy

Introduction

Protein ubiquitination, one of the most versatile of post-translational modifications, plays an important role in regulation of both proteolytic and non-proteolytic process, such as proteasomal or lysosomal degradation of targeted proteins, influencing protein activity, protein interactions and protein localization [1]. Ubiquitin modification includes the attachment of ubiquitin to target proteins by ubiquitinating enzymes, and the reversible ubiquitin removal, which is mediated by deubiquitinating enzymes (DUBs) [2, 3].

Ubiquitin is a highly conserved 76-amino acid polypeptide, and it is universally distributed among eukaryotes. The ubiquitin-protein conjugation system constitutes by cascades of steps including activating ubiquitin by the ubiquitin-activation enzyme (E1), then transfer the activated ubiquitin to the target proteins on a lysine residue by ubiquitin-conjugating enzymes (E2) and ubiquitin ligases (E3) [4, 5]. Sometimes, only one single ubiquitin is attached to one or multiple lysines (mono-ubiquitination), whereas in others, ubiquitin chains (poly-ubiquitination) is added to target proteins with each ubiquitin attached to the prior (**Figure 1**). Depending on the lysine for inter-ubiquitin linkages, ubiquitin chains are divided into several different types. As reported, lysine 6, (K6), K11, K27, K29, K33, K48, and K63 are used for chain formation. Among these, the best studyed is K63- and K48-linked ubiquitination. Polyubiquition chains linked by K48, and also K27, K6, K33, K11, and K29 mainly function during proteasomal degradation [6].

Ubiquitination of targeted proteins is reversed by deubiquitinating enzymes (DUBs), a superfamily of metalloproteases and cysteine prote-

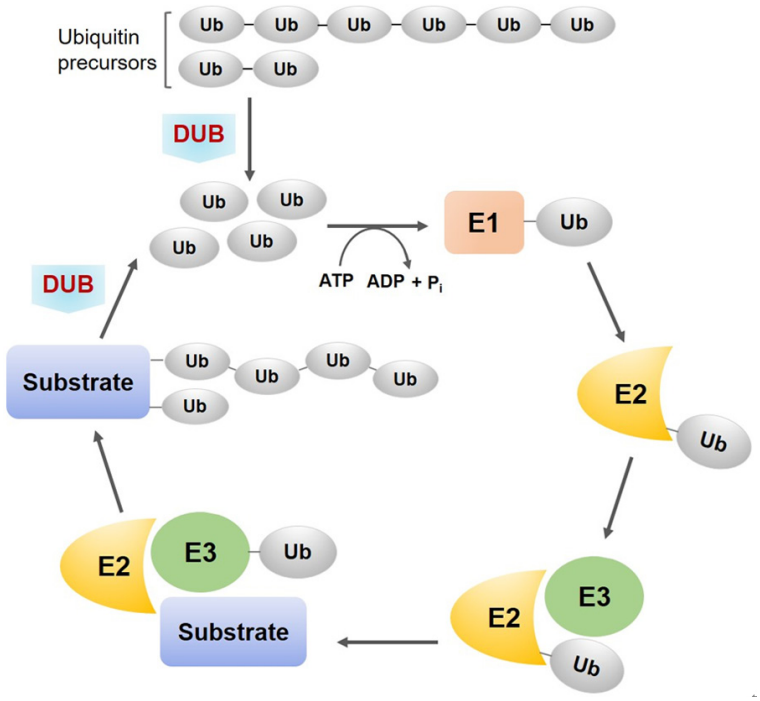

Figure 1. Ubiquitin ligases and deubiquitinases in the ubiquitination proteasomal system. Ubiquitin is firstly activated by the ubiquitin-activating enzyme (E1), followed by its transfer to a lysine residue on target proteins by ubiquitin-conjugating enzymes (E2) and ubiquitin ligases (E3). DUBs reverse this process by cleaving monoubiquitin or polyubiquitin chains from substrates, and therefore prevent proteins from degradation.

ases that catalytically cleave ubiquitin-protein bonds [7]. Up to date, more than one hundred human DUBs have been identified. Based on sequence and conserved domain, they can be classified into six families including ubiquitin-specific proteases (USPs), ovarian tumor proteases (OTUs), ubiquitin carboxy-terminal hydrolases (UCHs), Machado-Joseph disease protein domain proteases (MJDs), JAMM/MPN domain-associated metallopeptidases (JAMMs), and the monocyte chemotactic protein-induced proteases family (MINDYs) [8-11]. USPs, UCHs, OTUs, MJDs and MINDYs are cysteine peptidases, while JAMMs are zinc metallopeptidases [12].

DUBs regulate proteasomal or lysosomal degradation, proteins localization and recycling, which is crucial for protein homeostasis and normal functioning of the cell. Growing evidence indicates dysfunction of DUBs leads to amounts of genetic and sporadic diseases. For example, BRCA1-associated protein 1 (BAP1), one of the UCH family member, is mutated in mesothelioma, melanoma and renal cell carcinoma [13]; USP6 was reported to be translocated in aneurysmal bone cysts [14]; USP7 has shown mutation in neurological disorders [15]; USP8 is found to mutate in Cushing disease [16, 17]; USP9X cause developmental disorders with mutation [18] and shows dysregulated expression in cancer [19]. CYLD, commonly mutated in cylindromatosis [20]; and USP15 is indicative of amplification in certain glioblastoma, ovarian and breast cancers [21]. In addition, expansion of DNA 'CAG' trinucleotide repeats in ataxin 3 (ATXN3) leads to Machado-Joseph disease (also called spinocerebellar ataxia 3) [22]. Moreover, mutations in the JAMM family member result in microcephaly-capillary malformation syndrome [23]. More and more interest has been focusing on exploiting the regulation of DUBs on vital proteins and pathways involved in cancers. In this paper, we mainly focus on the role of DUBs in liver cancer.

DUBs involved in human liver cancer

Plenty of DUBs have displayed tumour-suppressing or tumor-promoting functions, and therefore may represent potential drug targets for treatment [24]. DUBs related to liver cancer progression are primarily discussed below.

CYLD

CYLD, a K63 linkage-specific deubiquitinase, is one unique member of the USP family, whose zinc finger domain responsible for distal ubiquitin interaction was deleted. The cylindromatosis gene (CYLD) was reported to suppress tumor, whose mutation was found in familial cylindromatosis (also known as Brooke-Spiegler syndrome), an autosomal-dominant predisposition to various tumors of the skin appendages [25].

CYLD is an essential modifier of NF-κB signaling and the ubiquitination state of the NF-κB-

activating molecule NEMO [26]. During liver tumorigenesis, CYLD function as tumour suppressor. By conditional knockout of CYLD in parenchymal liver cells, Bergkamen et al. reported the mutant CYLD in CYLDxAlbCre animals resulted in a chronic inflammatory response characterized by prominent ductular reaction and biliary fibrosis. NF-κB signaling was demonstrated to increase in livers of CYLD (FF) xAlbCre mice and may contribute to the fibrotic and inflammatory response. CYLD-mutant form did not contribute to spontaneous hepatocellular carcinomas (HCC), but showed a significantly increased sensitivity to liver cancers induced by the chemical carcinogen diethylnitrosamine (DEN), which proved to be associated with sustained c-Jun N-terminal kinase 1 (JNK1)-mediated signaling by ubiquitination of TNF receptor-associated factor 2 and expression of c-MYC [27, 28]. Through regulation the level of hepatocyte growth factor, CYLD alleviated liver damage and hepatocellular fibrogenesis [29]. Once expressing a deubiquitinase-deficient form of CYLD, which has similar oncogenic mutations in humans, it leads to spontaneous hepatic fibrosis and liver tumours by activation of c-Jun N-terminal kinase (JNK) and TGF-β activated kinase 1 (TAK1) [30, 31]. Overexpression of CYLD in hepatocytes inhibits both inflammation and fibrosis in mice with nonalcoholic steatohepatitis, whose progression lead to liver cancer finally [32].

In addition, CYLD is suggested to involve in the apoptosis resistance of hepatocellular carcinoma cells by enhancing NF-κB activity [33]. Therefore, CYLD plays key roles in liver inflammation and cancer. It represents a promising therapeutic target for liver cancer.

UCHs

UCHs have recently drawn much attention because of their diverse functions in cell biology [34, 35]. Until now, four members of UCHs have been identified including UCH-L1/PGP9.5 (protein gene product 9.5), UCH-L3, UCHL5/UCH37, and BRCA1-associated protein-1 (BAP1) [36-39]. The biological effects of the four UCH enzymes are complicated, as these proteins play quite different roles in different tumor progression.

UCHL1: UCHL1 has been studied extensively. Yu et al. showed hypermethylation of UCHL1 promoter CpG downregulated or silenced its expression in liver cancer, which provided tumor suppression evidence of UCHL1. Previous study has demonstrated that UCHL1 can directly interact with p53 and stabilize p53 through its hydrolase activity, and then decrease MDM2 by its E3 ligase activity. Subsequently, UCHL1 increases the p21 expression in HCC cells, resulting in G2/M phase arrest and hence suppressing proliferation. Moreover, re-expression of UCHL1 activates caspase-9 and induces PARP cleavage, leading to cell apoptosis [40].

Recently, the methylation level of UCHL1 was observed higher in tumor tissues compared with adjacent normal tissues. Cholangiocarcinoma patients with low methylation of UCHL1 survived longer overall, indicating the methylation level of UCHL1 may represent a potential biomarker for Cholangiocarcinoma prediction [41]. Yang et al. reported upregulation of UCHL1 gene promoted apoptosis in hepatocellular carcinoma cells treated with adriamycin and verapamil, while UCHL1 knockdown by siRNA weakened the effect, indicating UCHL1 was involved in the reversal effect of verapamil on Adriamycin-resistant hepatocellular carcinoma cells by promoting apoptosis [42].

UCH37: UCH37 has unique isopeptidase activity of the 19S proteasome complex, which is special for the UCH members. As one subunit of the 19S regulatory particle, hRpn13 interacted with UCH37 via KEKE motifs in the C-terminal regions, then UCH37 is recruited and activated to show deubiquitination activity [43-47]. Fang et al. firstly observed higher UCH37 expression in liver cancer tissues than adjacent para-cancerous tissues, which indicated UCH37 could be a predictor of recurrence after radical resection in HCC patients. Moreover, UCH37 promoted migration and invasion of HCC cells by deubiquitination of PRP19 (essential RNA splicing factor) [48]. By a functional proteomic analysis and screening, glucose-regulated protein 78 was identified as UCH37-interacting protein in HCC, but how the interaction regulates HCC progression remains further investigation [49].

BAP1: It has been found that BAP1 associates with multi-protein complexes that regulate key cellular pathways, including the cell differentiation, cell death, cell cycle, and the DNA damage response (DDR) [50]. Recently, Mosbeh et al. suggested that BAP1 may regulate the patho-

genesis of biliary and pancreatic cancers, a subset of hepatocellular carcinoma. High frequency of BAP1 loss in intrahepatic cholangicarcinoma was identified, while the frequency was lower in hepatocellular carcinoma and extrahepatic biliary cancer. For HCC tumors with decrease or loss of BAP1, expression of bile duct (cytokeratin 7) and hepatocytic (HepPar1) markers were higher than those with preserved BAP1 [51]. These studies all indicate BAP1 may be a novel therapy target.

USP9X

USP9X, which belongs to the X-linked USP family, can remove mono-ubiquitin and a number of ubiquitin chains, such as K29, K48 and K63 linkages [52-56]. It has been found to interact with more than 35 proteins. By regulating the protein claspin during S phase [57], USP9X maintains DNA damage checkpoint responses and DNA replication fork stability. Long noncoding RNA LNC473 enhanced HCC cell proliferation, invasion and epithelial-mesenchymal transition process by recruiting USP9X to survivin, which lead to increased survivin expression, a result of ubiquitination inhibition [58]. Overexpression of miR-26b inhibited the endogenous expression level of USP9X protein, leading to the epithelial-mesenchymal transition inhibition of hepatocytes [59]. Above studies indicate USP9X may be a crutial factor involved in epithelial-mesenchymal transition process of HCC. Also, USP9X palys roles in cell death. Zhang et al. reported that glycogen synthase kinase-3β (GSK-3β), a multifunctional kinase, suppressed hydrogen peroxide (H_2O_2)-induced cell death in HepG2 cells through inhibition of USP9X, and subsequently ubiquitination and proteasome-dependent degradation of ASK1 [60]. HCC cells with p53 expression showed enhanced response to combined treatment with WP1130, inhibitor of USP9X, and doxorubicin compared with p53-deficient cells. Mechanistically, USP9X inhibition promoted ubiquitin-proteasome dependent degradation of p53 [61]. Taken together, USP9X represents another potential therapeutic target.

USP7

USP7, also known as HAUSP, is an evolutionarily conserved protein that was first identified as a molecular partner of the herpes simplex virus protein, Vmw110 [62]. USP7 is required for cell growth, development and stress [63]. In human HCC tissues, the expression of USP7 is higher than in matched peritumoral tissues. Ectopic expression of USP7 promotes HCC cells growth both *in vitro* and *in vivo*. Mechanistically, USP7 overexpression stabilizes thyroid hormone receptor-interacting protein 12 (TRIP12) by deubiquitination, thus constitutively inactivating the tumor suppressor p14 (ARF) [64]. Zhu et al. identified that in HCC cells, USP7 protein level was inhibited by microRNA-205 (miR-205), thereby impairing the p53 signaling pathway and facilitating cell proliferation [65]. Moreover, by facilitating the interaction of USP7 with p53, Abraxas brother 1 suppresses HCC cell proliferation and tumour formation [66]. Base on above, USP7 may play vital role during HCC development, which needs further evidence.

A20

A20, also known as TNFAIP3 (Tumor necrosis factor α-induced protein 3), is originally discoved as a primary gene product after tumor necrosis factor α (TNFα) treatment in human umbilical vein endothelial cells [67]. A20 hydrolyzes K48, K11 and K63 polyubiquitin, while it displays enhanced activity towards K63-polyubiquitinated substrates in cells [68-71]. It has been shown that A20 is an important regulator of cellular inflammation signaling [72]. Over the past few years, growing evidence suggests that A20 also plays a functional role in cancer development. Catrysse et al. showed the mice lacking A20 specifically in liver parenchymal cells spontaneously develop chronic liver inflammation, hepatocyte apoptosis and lethality following treatment with sublethal doses of TNF. Besides, these mice are more susceptive to hepatocellular carcinoma development induced by chemical or high fat-diet [73]. Another study revealed silence of A20 accompanied with IFN-γ exposure obviously repressed cell viability, and induced cell-cycle arrest and apoptosis in HCC cells through restraining phosphoinositide 3-kinase/Akt pathway and antiapoptotic B-cell lymphoma 2 proteins [74].

In addition, A20 plays a role in HCC metastasis. In 89 tissue samples from HCC patients, the expression of A20 was decreased in invasive cells compared with the noninvasive cells. Overexpression of A20 significantly inhibited

the proliferation, epithelial-mesenchymal transition and migration of HCC cells both *in vitro* and *in vivo* [75, 76].

Interestingly, Chen et al. found patients with higher A20 expression had a prolonged overall survival and disease-free survival than those with lower A20 expression [76]. Meanwhile, a recent study showed in HCC and liver cirrhosis patients, A20 mRNA level in peripheral blood mononuclear cells was higher than patients with chronic hepatitis B, who showed significantly higher A20 mRNA level than the healthy. For HCC patients with vascular invasion, liver cirrhosis and ascites, A20 mRNA level was also elevated compared with those without [77]. Therefore, A20 might represent a potential biomarker to differentiate the stages of HCC and evaluate prognosis.

Other DUBs involved in liver cancer

There are growing DUBs reported to promote HCC progression recently. By unbiased siRNA screening, Kim et al. found that YOD1 enhances the stability of ITCH, an E3 ligase of LATS, and facilitates LATS1/2 ubiquitination and degradation, subsequently increasing YAP/TAZ levels. Overexpression of YOD1 enhances the hepatocytes proliferation and leads to hepatomegaly [78]. It has been shown that the expression of USP14 in tumor tissues of HCC patients was much higher than para-carcinoma and normal liver tissues. Knockdown or inhibiton of USP14 with b-AP15, the potent and selective inhibitor of USP14, in human hepatocarcinoma SMMC7721 cells both significantly suppressed cell proliferation and induced apoptosis [79, 80]. USP4 was up-regulated in mesenchymal-type liver-tumor cells, facilitating proliferation and migration [81]. Downregulation of USP39 significantly enhanced apoptosis, inhibited cell growth in HCC cells, and reduced xenograft tumor growth in nude mice [82, 83]. By directly targeting and inhibiting USP28, miR-363-3p destabilizes Myc and prevented hepatocellular tumorigenesis [84]. The EEF1A2/PI3K/AKT/mTOR axis has been suggested to promote the protumorigenic stabilization of the protooncogene MDM4 in human HCC by way of USP2a and AKT-mediated phosphorylation [85].

However, other DUBs have emerged as tumor suppressor. For example, USP16 was frequently downregulated in human HCCs, and the reduced expression of USP16 was correlated with poor differentiation status. In tumour cells, Inhibition of USP16 promoted stem-like properties, ectopic expression of USP16 significantly decreased cell viability and tumour growth [86]. DUBs also regulate drug resistance, which has been a challenge during cancer treament. USP22 promotes the multidrug resistance in HCC cells by activating the SIRT1/AKT/MRP1 pathway via direct interaction with SIRT1 and upregulation of SIRT1 protein [87]. In chemoresistant HCC cells, silencing USP22 dramatically suppressed tumorigenic and metastatic capacities in vivo, as well as inhibited proliferation and epithelial-mesenchymal transition in vitro [88].

DUBs may represent valuable biomarker for HCC patients in near future. HCC samples with higher OTUB1 and USP11 expression have shorter overall survival time [89, 90]. HCC patients with Cezanne reduction, in which cancer cells showed high invasiveness, had shorter time to recurrence and poor overall survival [91]. HCC patients with high expression of USP22 showed poor prognosis, reduction of USP22 suppressed cell growth [92]. Tumor metabolism is the key event for unconstrained proliferation of tumor cells. DUBs may impact this process to alter HCC progression. USP2a inhibited fatty acid synthase ubiquitination and subsequently promoted lipogenesis and HCC development [93].

Development of DUBs inhibitors for cancer therapy

Bortezomib, the proteasome inhibitor, has been approved by FDA for multiple myeloma treatment, which makes the ubiquitin-proteasome system as a promising target for new anticancer treatment development [94]. Considering the key roles of DUBs in the ubiquitin-proteasome system and diverse functions in cancer, growing interest has been focused on exploiting DUBs as therapeutic targets [95]. However, the development of selective DUBs inhibitors has been hampered by lack of sufficient knowledge about DUBs biology, difficulties in establishing suitable biochemical methods for compound screening, limitations in models of *in vitro* and *in vivo* to measure DUBs activity. Over the past few years, the progress in DUBs drug discovery has accelerated with many issues overcome. Although no DUBs inhibitors have successfully entered clinical trials yet, endeav-

or is being made to develop them as treatment strategies.

Currently, both pan-DUBs inhibitors and specific inhibitors of single DUB have been identified. The first DUBs active-site inhibitors were cyclopentenone prostaglandins, which induce accumulation of polyubiquitylated proteins and cause p53-dependent apoptosis in colon cancer cells [96, 97]. P5091, the inhibitor of USP7, lead multiple myeloma cells to apoptosis [98]. WP1130, which inhibits USP5, USP9X, USP14, and UCH37, was found to trigger rapid polyubiquitinated proteins accumulation in aggresomes and induced apoptosis of tumor cell [99].

In brief, the development of DUBs inhibitors are in the early stages and numerous researches have proved selective inhibitors of cancer-promoting DUBs, such as USP7, efficiently induced cancer cell death. More efforts need to be made for improving the specificity, efficacy, and safety. There is no doubt DUBs inhibitors are emerging as attractive druggable targets and new agents for the treatment of cancer.

Conclusions and perspectives

Liver cancer is predicted to be the fourth leading cause of cancer death worldwide in 2018 and therefore a major public health challenge. Because of rapid progression and lack of targeted drugs, the survival rate of liver cancer is extremely low. Recently, growing evidence has demonstrated the vital role of DUBs in liver cancer progression, which may represent novel targets for cancer therapy. With dramatic advances in DUB screening technologies and biochemical assays, increasing numbers of DUB inhibitors have been developed. Such inhibitors provide the basis for drug-like molecules suitable for clinical evaluation and also provide versatile tools to further investigate DUB cell biology.

Although much progress has been made in exploring the roles of DUBs in liver cancer progression, why these DUBs function differently in the same disease needs further investigation. And we know little about what function the same one DUB has through the pathological process, including liver fibrosis, liver cirrhosis and final hepatocellular carcinoma. In addition, knowledge about whether DUBs affect the tumor microenvironment during liver cancer progression is deficient. Also, specificity and selectivity of DUBs inhibitors needs improvement. Summary, we will witness rapid expansion in the arenas of DUB biology and drug discovery in the next few years.

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Disclosure of conflict of interest

None.

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